

BIOCHEMISTRY

BILIRUBIN'S ROLE

Proposed redox cycle explains heme product's antioxidant power

BILIRUBIN, A LINEAR heme product, is best known as the yellow pigment that causes jaundice. High bilirubin levels can cause brain damage and have other cytotoxic effects, especially in infants, but elevated levels in adults have been associated with a lower risk of cardiovascular disease and cancers. This mixed message of the physiological role of bilirubin has been puzzling.

Now, graduate student David E. Barañano and neuroscientist Solomon H. Snyder of Johns Hopkins University School of Medicine and coworkers have uncovered a redox cycle involving bilirubin that consumes high concentrations of peroxyl radicals. This cycle is thought to be the solution to the puzzle, explaining how bilirubin affords powerful protection for cells [*Proc. Natl. Acad. Sci. USA*, 99, 16093 (2002)].

Bilirubin is the terminal product of the breakdown of heme, the iron porphyrin molecule that carries oxygen in red blood cells. Heme is cleaved by heme oxygenase to form biliverdin, which in turn is reduced by biliverdin reductase to form bilirubin. Biliverdin is a green pigment that's water soluble and considered non-toxic. But the toxic bilirubin is insoluble and needs to have sugar groups added before it can be excreted. One missing piece of the puzzle had been why bilirubin is needed when biliverdin could be readily excreted.

Snyder's group had previously shown that the nanomolar concentrations of bilirubin found in cells can mitigate the effects of much higher concentrations of peroxyl radicals. To reconcile this apparent discrepancy in numbers, Snyder and his colleagues reasoned that bilirubin might be part

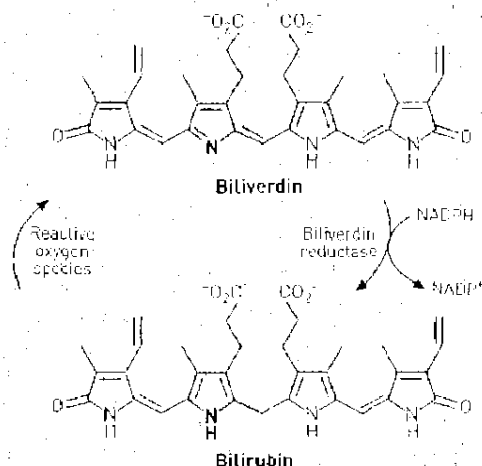
of a cycle that is constantly being replenished.

The researchers developed a model in which they propose that bilirubin, in a previously unknown step, is oxidized back to biliverdin by peroxyl radicals. To test their hypothesis, they used RNA interference to inhibit biliverdin reductase and exposed human cancer cells and rat brain cells to hydrogen peroxide. Without bilirubin being produced, the cells suffered a high rate of damage and death. When the enzyme was not inhibited, bilirubin was produced and the cells survived—even at a 10,000-fold excess of H_2O_2 .

The cytoprotective effect of bilirubin is significantly better than glutathione, "the molecule believed for 80 years to be the most important cellular antioxidant," Snyder says. Since bilirubin is found only in low concentrations in cells but in higher

CYTOPROTECTION

Bilirubin can scavenge a 10,000-fold excess of peroxyl radicals by redox cycling



NADPH = nicotinamide adenine dinucleotide phosphate

concentrations in blood, it could be the major protector for cell membranes while glutathione may protect components inside cells, Snyder suggests.

Discovery of the redox cycle offers an explanation for the health benefits of bilirubin, and could lead to its therapeutic use, the researchers note.—STEVE RITTER

TRANSGENIC FOOD AND FEED

Legislation Seeks World's Strictest Labeling

After much wrangling, the European Council of Agricultural Ministers agreed on a law that would require new labels for genetically modified (GM) food and feed. If passed, the law would lead to the world's strictest labeling requirements for transgenic commodities.

Under the revised draft law, all food and feed that contains or is derived from transgenic plants must be labeled whether or not it contains DNA or protein of transgenic origin. Under current regulations, feed derived from transgenic plants and highly processed commodities, such as soybean oil and glucose from GM plants, does not have to be labeled.

With this new law, the European Commission hopes to persuade member states not to block applications to license GM products and

to lift the de facto moratorium on GM crops in effect in Europe since June 1999.

"This new law further ensures consumer choice through labeling of GMO [genetically modified organism]-derived food and also provides the farmer with information," says David Byrne, European commissioner for health and consumer protection. "There are no known adverse effects on human health from eating GMOs," he adds.

The revised draft law is not expected to end the European controversy over GM food. The U.K. voted against the draft, calling it too strict, and Austria and Luxembourg voted against it, saying it is not strict enough. The draft legislation will now be considered by the Environment Council and the European Parliament.—BETTE HILEMAN